PATENT SPECIFICATION

NO DRAWINGS

822,351

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International Classification:—C07d.

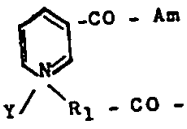
COMPLETE SPECIFICATION

New Quaternary Salts and their production

We, CILAG LIMITED, of 209 Hochstrasse, Schaffhouse, Switzerland, a Body Corporate organised under the Laws of Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new quaternary salts and their production.

The new quaternary salts of the invention are nicotinic acid amides of the general formula:



in which Am represents an unsubstituted amido group or an amido group substituted by an aliphatic, araliphatic or aromatic hydrocarbon residue, which araliphatic or aromatic residue may itself be substituted by halogen atoms and/or trifluoromethyl groups, Y represents an anion, R_1 represents an aliphatic radical containing not more than 3 carbon atoms, X represents oxygen or the NH group, R_2 represents an aliphatic, araliphatic or aromatic radical, which araliphatic or aromatic residue may be substituted by halogen atoms and/or trifluoromethyl groups.

The compounds of the invention were hitherto unknown. They are valuable disinfectants with a markedly strong lethal action on pathogenic skin fungi. The halogen substituted compounds also destroy insects which feed on keratin.

Simple quaternary salts of substituted and unsubstituted nicotinic acid amides have hitherto been known. Thus for example the production of 1 - alkyl - 3 - carbamyl - pyridinium - halides and 1 - alkyl - 3 - (dialkyl - carbamyl) - pyridinium - halides has been described by M. F. Zienty in J. Am. Pharm. Assoc. Sci. Ed. *37*, pp. 99—101 (1948). These compounds have a good inhibitory action on Staphlococcus aureus but have no action on pathogenic skin fungi such for example as Trychophyton interdigitale.

The new quaternary salts may be employed for treating fungus infections of the skin and mucous membranes, for example the mucous membranes of the mouth in the case of mycotic stomatitis (thrush). They can be employed for this purpose in the form of salves and tinctures.

A further important field of application is in the treatment of fungus infections of the internal organs, for example the lungs, kidney and bladder. For this purpose the compound can for example be applied by inhalation atomised in aqueous solution, by irrigation or intraperitoneally.

For the treatment of foot mycosis the new salts can be applied in conjunction with other antimycotics. For this purpose the N - alkyl - N - formyl - N - hydroxymethyl compounds have proved very effective. In addition to a good fungicidal action, the last mentioned compounds have a slight tanning action, which may be of great advantage in healing, since the mycotically attacked epidermis is very much softened. This tanning action strengthens the softened skin and makes it impermeable to further attack by the fungus.

The new quaternary salts can be prepared in various ways. The preferred method is to react nicotinic amide, or a nicotinic acid amide substituted in the carbamido group, with halogen-paraffin carboxylic acid esters or amides, or hydroxyparaffin acid esters or amides esterified with other strong acids.

For example nicotinic acid amide, nicotinic acid methyl amide, nicotinic acid ethyl amide, nicotinic acid allyl amide, nicotinic acid butyl amide, nicotinic acid decyl amide, nicotinic acid dodecyl amide, nicotinic acid cetyl amide, nicotinic acid benzyl amide, nicotinic acid *p*-chlorbenzyl amide, nicotinic acid anilide, nicotinic acid *p*-chloranilide, nicotinic acid 2:4-dichloranilide, nicotinic acid 3:4 - dichlor-

[*Price 3s. 6d.*]

anilide, nicotinic acid 3 - trifluormethylanilide, nicotinic acid dimethyl amide, nicotinic acid 3 : 5 - bis - trifluormethylanilide, nicotinic acid 3 - trifluormethyl - 4 - chloranilide, nicotinic acid diethyl amide, nicotinic acid morpholide, nicotinic acid piperidide or nicotinic acid pyrrolodide can be reacted with the hexyl, butoxyethyl, octyl, decyl, nonyl, undecyl, dodecyl, cetyl, benyl, phenyl, chlorphenyl or bromphenyl esters of chloracetic acid, bromacetic acid, chlorpropionic acid or chlor butyric acid, or with the corresponding halogen - acetic or halogen - propionic acid hexyl amides, undecyl amides, dodecyl amides, cetyl amides, anilides, chloranilides, toluidides, halogen - toluidides, trifluor - methyl - anilides or alkoxyanilides.

Nicotinic acid amide or substituted nicotinic acid amides can be reacted with chlor - acetic acid 3 - trifluoromethylanilide, chloracetic acid 3 - trifluoromethyl - 4 - chloranilide, chloracetic acid 4 - chlor - anilide or chloracetic acid 4 - chlor - phenyl ester.

The quaternary salts can be produced in the presence or absence of a solvent by simply mixing and heating the two reactants. In cases where the quaternising component is liquid, it can be used as the solvent.

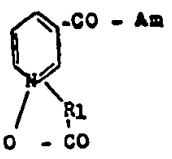
The anion X in the quaternary salts formed can if desired be replaced by another anion by reaction with a salt containing the same.

A further possible way of producing the quaternary salts is to treat nicotinic acid amides with ring destabilising compounds and to react the adducts with amino-paraffin carboxylic acid esters or amides.

The compounds which are used for rendering the ring unstable are the organic compounds of a strongly negative character containing halogen atoms which are specified in "Journal für praktische Chemie," Vol. 83, page 325, (1911) and "Das Pyridin und Seine Derivate," Maier-Bode and Altpeter, 1934, page 22, and analogues of these compounds in which the halogen atoms are replaced by a different halogen atom or by an alkylsulphonyloxy group or an alkoxy sulphonyloxy group. The ring destabilising compound may be, for example, dinitrochlorobenzene, cyanogen chloride or cyanogen bromide.

The corresponding mono Schiff's bases of glutaconic dialdehydes with amino carboxylic acid esters or amides can be treated with ring closing components, for example with hydrochloric acid in the absence of water, in order to produce the desired quaternary salts.

Another way of producing a certain class of the desired substances consists in treating betaines of the general formula:



with the desired alcohols or amines which contain the residue R_2 and if desired converting the pyridinium hydroxides so produced into their salts.

Another way of producing the new compounds is to convert a quaternary salt of nicotinic acid into its amide by a method known to be capable of converting a carboxylic acid into its amide, for example by first preparing the halide or ester and then reacting the latter with the desired amine AmH, or by reacting the quaternary salt of nicotinic acid with the amine under dehydrating conditions, for example in the presence of phosphorus pentoxide.

It is also possible to react carbamyl halides of the general formula: Am—Co Hal, or isocyanates of the general formula: Am = C = O with the quaternary salts of nicotinic acid, and this reaction gives a good yield of the desired products.

The following Examples illustrate the production of the new compounds of the invention:

EXAMPLE 1.

39 Gm. of nicotinic acid amide, 75 gm. of chlor-acetic acid decyl ester and 100 cc. of dioxane are heated with stirring for 13 hours to 100° C. After cooling the precipitated crystalline mass is slurried in approximately 1 litre of acetone and then filtered with suction and washed with acetone. The quaternary salt so obtained is dissolved in five times the quantity of ethanol, filtered and treated hot with the same volume of ethyl acetate.

In this way there are obtained 80 gm., i.e. 70% of the theoretical yield, of 3-carbamido-N_1 - (carbodecyloxy) - methyl - pyridinium - chloride, melting with decomposition at 142—144° C.

EXAMPLE 2.

The compound described in Example 1 could also be obtained as follows:

40 Gm. nicotinic acid amide and 200 gm. 2,4 - dinitro - chlorobenzene are heated together to 100° C. for 1—2 hours. The mass obtained is dissolved in 300 cc. methanol and the resulting solution is filtered; ether is added to the filtrate until recrystallisation begins. In this way, between 60 and 80 gm. of 3 - carbamido - N_1 - (2,4 - dinitrophenyl) - pyridinium chloride, melting at 75° C. are obtained. This compound can easily be purified by dissolution in, and precipitation from, a methanol/ether mixture.

20 Gm. of the adduct obtained are heated for 3 hours to the boiling point with 15 gm. of aminoacetic acid decyl ester in 200 cc. dioxane. The solution obtained is evaporated, and the residue is stirred with 200 cc. water. The mixture obtained is cooled; the 2,4 - dinitro - aniline which separates out is filtered off with suction and the filtrate is evaporated. After recrystallisation of the residue from an ethanol/ethyl acetate mixture, 22 gm. of 3 - carb - amido - N_1 - (carbodecyloxy) - methyl - pyrid-

inium chloride are obtained. The melting point is 142—144° C. with decomposition.

EXAMPLE 3.

105 Gm. of 3 - carbamido - N_1 - (carbo - hexyloxy) - methyl - pyridinium - chloride, melting at 143—144° C. are obtained from 90 gm. of chloracetic acid hexyl ester and 61 gm. of nicotinic acid amide in 100 cc. of dioxane.

EXAMPLE 4.

3 - Carbamido - N_1 - (carbododecyl) - methyl - pyridinium - chloride, melting at 151—153° C. with decomposition, is obtained in a yield of 73% from 147 gm. of chloracetic acid dodecyl ester and 69 gm. of nicotinic acid amide in 150 cc. of dioxan.

EXAMPLE 5.

32.8 Gm. of nicotinic acid amide and 70 gm. of chloracetic acid lauryl amide are heated in 100 cc. of dioxan for 15 hours to 100° C. and the reaction mass after cooling is diluted with ether. 80 to 85 Gm. of 3 - carbamido - N_1 - (carbododecylamido) - methyl - pyridinium - chloride are obtained. This new compound can readily be recrystallised from ethanol and melts at 202—204° C.

EXAMPLE 6.

60 Gm. of nicotinic acid *p* - chloranilide and 65 gm. of chloracetic acid dodecylester are heated in 200 c.c. of dioxan for several hours with mechanical stirring to 100° C. 3- N_2 - p - chlorphenyl - carbamido - N_1 - (carbodecyloxy) - methyl - pyridinium - chloride (which decomposes at 190—191° C.) is obtained in 60% yield.

EXAMPLE 7.

3 - Carbamido - N_1 - [carbo - (4 - chlor - phenylamido)] - methyl - pyridinium - chloride of decomposition point 262—263° C. is obtained in 34% yield by heating equimolecular quantities of nicotinic acid amide and chloracetic acid 4 - chloranilide.

EXAMPLE 8.

1 Mol of nicotinic acid dodecylamide and 1 mol of chloroacetic acid - *p* - chlorphenyl ester are heated in dioxane. On cooling beautiful leaf-shaped crystals of 3 - dodecyl - carb - amido - N_1 - [carbo - (*p*- chlorphenoxy)] - methylpyridinium chloride are obtained.

EXAMPLE 9.

By heating 1 mol of nicotinic acid amide and 1 mol of α - methane - sulphonyloxy - propionic acid undecyl amide in dioxan or xylene, 3 - carbamido - N_1 - α - carbo - (undecylamido) - ethyl - (2) - pyridinium - methane - sulphate is obtained in iridiscent leaflets.

EXAMPLE 10

By heating 1 mol of nicotinic acid allyl amide with 1 mol of chloracetic acid hexyl-ester, 3 - N_2 - allyl - carbamido - N_1 - (carbo-hexyloxy) - methyl - pyridinium - chloride is obtained in good yield.

EXAMPLE 11

By heating 1 mol of nicotinic acid 4-aceto-acetylamino - anilide and 1 mol of bromo-acetic acid dodecyl ester, 3 - N_2 - (4 - aceto-acetyl - aminophenyl) - carbamido - N_1 - carbododecyloxy) - methyl - pyridinum - bromide is obtained in almost quantitative yield.

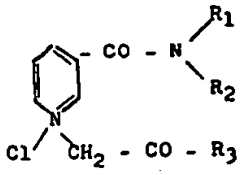
EXAMPLE 12

Equivalent quantities of nicotinic acid 3-trifluor - methyl - 4 - chloranilide and chlor-acetic acid undecyl amide are heated together to boiling in xylene or dioxan for several hours. On cooling 3 - carbo - (3^1 - trifluoro - methyl - 4^1 - chloranilido) - N_1 - (carboundecylamido) - methyl - pyridinium - chloride crystallises in beautiful leaflets.

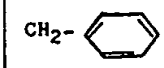
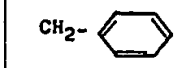
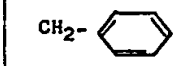
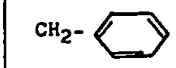
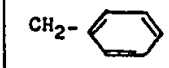
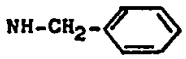
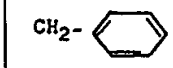
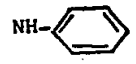
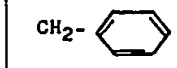
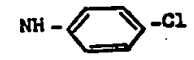
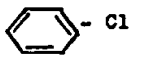
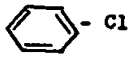
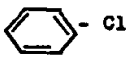
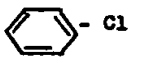
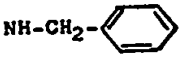
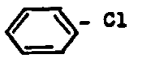
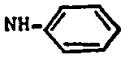
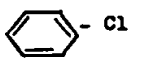
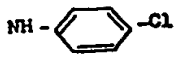
EXAMPLE 13

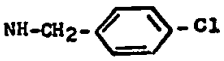
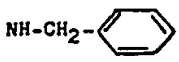
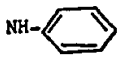
Equivalent quantities of nicotinic acid amide and chloracetic acid 4 - chlor - 3 - trifluoro - methylanilide are heated together in dioxane on the water bath for several hours. After cooling, the same volume of acetone is added and the crystals are filtered off with suction. In this way 3 - carbamido - N_1 - (carbo - [4-chlor - 3 - trifluoromethyl - anilido] - methyl)-pyridinium - chloride is obtained in good yield.

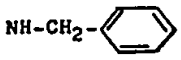
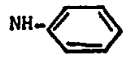
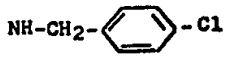
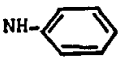
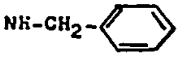
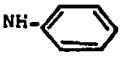
Compounds of the general formula:

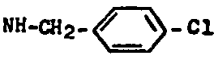
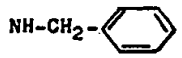
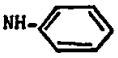


set out in the following table are obtained in manner analogous to that described in Examples 1 to 13.

R_1	R_2	R_3	m.p.	Yield
H		NH—$C_{10}H_{21}$(n)	129—130° C.	67.5%
H		NH—$C_{12}H_{25}$(n)	131—132° C.	74.3%
H		O—$C_{12}H_{25}$(n)	108—109° C.	60%
H		O—$C_{10}H_{21}$(n)	112—113° C.	60%
H			162—163° C.	76.5%
H			188—189° C.	66%
H			191—192° C.	67%
H		NH—$C_{10}H_{21}$(n)	210—211° C.	64.3%
H		NH—$C_{12}H_{25}$(n)	207—208° C.	81%
H		O—$C_{10}H_{21}$(n)	188° C. /Dec.	70.5%
H			241—243° C.	65.8%
H			239—240° C. /Dec.	47.5%
H			237—239° C. /Dec.	49.5%

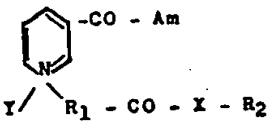
R_1	R_2	R_3	m.p.	Yield
H		$NH—CH_2—CH=CH_2$	207—208° C. /Dec.	64.6%
H	$CH_2—CH=CH_2$	$NH-C_{10}H_{21}(n)$	81—83° C.	67%
H	$CH_2—CH=CH_2$		171—173° C.	75.3%
H		$NH-C_{10}H_{21}(n)$	183—185° C.	29.1%
H		$NH-C_{12}H_{25}(n)$	197—198° C.	51.7%
H		$O—C_{12}H_{25}(n)$	173—174° C.	62.5%
H		$O—C_{10}H_{21}(n)$	170—171° C.	55%
H			247—248° C. /Dec.	37.5%
H			233—235° C.	74%
H			250° /Dec.	65%
H		$NH—CH_2—CH=CH_2$	203—204° C.	51.5%
H			279—280° C. /Dec.	47%
H		$O—C_{11}H_{23}(n)$	172—174° C.	46.5%
CH_3	CH_3	$NH—C_{10}H_{21}(n)$	108—110° C.	62.7%
CH_3	CH_3	$NH—C_{12}H_{25}(n)$	119—120° C.	75.4%

R_1	R_2	R_3	m.p.	Yield
CH_3	CH_3		203—204° C.	49.5%
CH_3	CH_3		168—169° C.	81%
CH_3	CH_3		244—245° C. /Dec.	61.5%
C_2H_5	C_2H_5	$NH—C_{10}H_{21}(n)$	105—106° C. Hygrosc.	39%
C_2H_5	C_2H_5	$NH—C_{12}H_{25}$	98—100° C. Hygrosc.	50.2%
C_2H_5	C_2H_5		153—155° C.	61%
C_2H_5	C_2H_5		180—181° C.	86.5%
C_2H_5	C_2H_5		207—208° C.	76%
H	CH_3	$NH—C_{10}H_{21}(n)$	133—134° C.	78%
H	CH_3	$NH—C_{12}H_{25}(n)$	145—146° C.	78%
H	CH_3	$O—C_{12}H_{25}(n)$	89—90° C.	50%
H	CH_3	$O—C_{10}H_{21}(n)$	73—75° C.	45%
H	CH_3		128—132° C.	74%
H	CH_3		207—209° C.	47.5%
H	CH_3	$NH—CH_2—CH=CH_2$	80—84° C. Hygrosc.	29%
H	CH_3		259° C. /Dec.	71%
H	CH_3	$O—C_{11}H_{23}(n)$	79—81° C. hygrosc.	31%

R_1	R_2	R_3	m.p.	Yield
H	H	$NH—C_{10}H_{21}(n)$	207—208° C.	62%
H	H		245—246° C. /Dec.	39.2%
H	H		205—206° C.	52.5%
H	H		214—216° C.	60.5%
H	H	$NH—CH_2—CH=CH_2$	172—174° C. hygrosc.	25%
H	H	$O—C_{11}H_{23}(n)$	132—135° C.	33.8%
H	H	$O—CH_2—(CH_2)_8—CH=CH_2$	139—142° C.	3.7%
H	H	$O—C_{16}H_{33}$	170° C. /Dec.	71%
H	H		175° C. /Dec.	65%

WHAT WE CLAIM IS:—

1. Quaternary salts of nicotinic acid amides of the general formula:



in which Am represents an unsubstituted amido group or an amido group substituted by an aliphatic, araliphatic or aromatic hydrocarbon residue, which araliphatic or aromatic residue may itself be substituted by halogen atoms and/or trifluoromethyl groups, Y represents an anion, R_1 represents an aliphatic radical containing not more than 3 carbon atoms, X represents oxygen or the NH group, R_2 represents an aliphatic, araliphatic or aromatic radical, which araliphatic or aromatic residue may be substituted by halogen atoms and/or trifluoromethyl groups.

2. The quaternary salts of the general formula defined in Claim 1, and described in the foregoing Examples 1 to 13.

3. The quaternary salts of the general formula defined in claim 1, and described in the foregoing Table.

4. A process for the production of a quaternary salt of the general formula defined in Claim 1, wherein a nicotinic acid amide is reacted with an ester of a strong acid, and a hydroxy carboxylic acid ester or amide.

5. A process for the production of a quaternary salt of the general formula defined in claim 1, wherein a nicotinic acid amide is treated with a ring destabilising agent and the adduct obtained is reacted with an amino paraffin carboxylic acid ester or amide.

6. Processes for the production of quaternary salts of the general formula defined in claim 1, substantially as described with reference to each of Examples 1 to 13.

ELKINGTON AND FIFE,
Consulting Chemists and Chartered Patent Agents,
Bank Chambers, 329, High Holborn,
London, W.C.1.
Agents for the Applicants.

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